UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/132,799	08/13/98	SCHOENROCK U	BEIERSDORF-5

HM22/0526

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EXAMINER	
BORIN, M	
ART UNIT	PAPER NUMBER
1654	5

DATE MAILED: 05/26/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/132,799	Applicant(s) Schoenrock et al.
	Examiner M. Borin	Group Art Unit 1654

Responsive to communication(s) filed on _____.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-10* is/are pending in the application.

Of the above, claim(s) *2, 5, and 7-10* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1, 3, 4, and 6* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-10 are pending.

Restriction/Election Requirement

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1,3-6 drawn to cosmetic or pharmaceutical preparations, classified in class 514, subclass 18.

II. Claims 2,7-10, drawn to method of treatment skin pigmentation, classified in class 424, subclass 62.

The inventions are distinct because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different processes such as blood pressure regulation. Further, the method of use can be practiced with a broad variety of depigmenting agents other than claimed peptides, for example, with signal proteins of agoutis, or hydroquinone. The groups are differently classified and require non-coextensive patent and literature searches.

Because these inventions are distinct for the reasons given and have acquired a separate status in the art as shown by their different classification, and because of their recognized

divergent subject matter, and the necessity for non-coextensive literature searches restriction for examination purposes as indicated is proper.

If applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. MPEP 821.04.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Upon election of any single one of the Groups from above the following election of species is hereby required:

Species Requirement

The claims of Group are individually or dependently directed to a plurality of disclosed patentably distinct species of peptide monomers and their homo- and hetero- dimers, trimers and tetrameres. For the purposes of original examination on merits applicant is required to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

To be complete, a response to the election of species requirement should include a proper election along with a listing of all claims readable thereon, including any claims subsequently added. MPEP 809.02(a).

During a telephone conversation with Attorney S. Ryan on 04/10/99 a provisional election was made without traverse to prosecute the invention of Group I, claims 1,3-6. Affirmation of this election must be made by applicant in responding to this Office action. Claims 2,7-10 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

In regard to the election of species requirement, applicant elected, without traverse, monomer oligopeptide species of example 4 (Ac-VVRP-NH_2 ; p. 37). Claims reading on the elected species are claims 1, 3, 4, 6. Claim 5 is withdrawn from consideration as drawn to non-elected species. Claims 1,3,4, 6 are examined on merits to the extent they read on the monomer oligopeptide VVRP, its amide and/or N-acetyl derivative. To expedite the prosecution, prior art pertinent to some of the

non-elected species which has been found in the course of search of the elected species is applied as well.

Sequence Listing

2. This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because it does not contain a computer readable form and a paper copy of Sequence Listing. Applicant must provide a computer readable form (CRF) copy of the Sequence Listing, a paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 CFR 1.825(a) and (b).

Claim Objections

3. Claim 1: The use of term "homo- or hetero- monomer" in claim 1(1) is noticed. Terms "homo-" or "hetero-" are applicable for description of polymers (e.g., dimers, trimers, etc), not monomers.

Appropriate amendment is requested.

Claim Rejections - 35 U.S.C. § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3, 4, 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

A. The phrase "distinguished by" in claim 1, line 2, is vague and indefinite. The meaning of the phrase is not clear. Use of the language "consisting" or "comprising" is recommended. For the purposes of initial examination on merits the claims are considered as drawn to compositions "comprising" active ingredient as claimed.

B. Claims 1 and 6 recite broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation in the same claim. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86

USPQ 481 (Bd. App. 1949). In the present instance, claim 1, item (2), recites the broad recitation of Markush group of substituents for valine residue, and the claim also recites alanine as preferred substitution which is the narrower statement of the limitation. Further, claim 6 recites both broad and narrow concentration range limitations.

Claim Rejections - 35 U.S.C. § 102 and 103.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States..

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al (Agric. Biol. Chem., 54, 835-836, 1990).

The instant claims, in part defined in claim 1, items (1) and (3), are drawn to preparations comprising peptide VVRP, or peptides comprising said sequence VVRP.

Kohmura

Kohmura et al. describe fragments of human κ casein, in particular peptide having sequence VVRP (i.e., a peptide of the instant invention). See p. 835, Table 1, compound No. 6. Further, the reference teaches peptides comprising said sequence VVRP: AVVRP, PAVVRP, NPAVVRP, ANPAVVRP, YANPAVVRP (i.e., peptides as instantly claimed, wherein $\psi = 1 \div 5$, $\Omega = 0$). See p. 835, Table 1, compounds No. 7-11. The referenced peptides exhibit a strong inhibitory effect on angiotensin-converting enzyme (ACE), the latter being an important regulator of blood pressure (see, e.g., p.835, second column). Kohmura does not teach administration of the referenced peptides in a form of pharmaceutical composition.

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to prepare a pharmaceutical composition comprising peptides of Kohmura as an active ingredient, because Kohmura teaches that these peptides inhibit ACE activity and, therefore, may be useful in treatment of ACE-mediated processes, such as regulation of blood pressure. Further, the courts held that it is well known without citation of authority that drugs and pharmaceuticals are usually dispensed in either liquid or solid carriers. One of primary skills in the art would have known

that compound "X" would have had to be formulated in some manner so as to make it useful pharmaceutically. In re Rosicky, 125 USPQ 341 (CCPA 1960). Anyone would be capable of preparing a composition from a known compound. See, e.g., "Remington Pharmaceutical Sciences", part 8, Mack Publishing Co., Easton, PA, 1980.

7. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al, supra., and further in view of Atlas of Protein Sequence and Structure (Vol. 5, 1972).

The instant claims, in part defined in claim 1, item (2), are drawn to compositions comprising oligopeptide VVRP wherein one of Val residues is replaced by leucine or isoleucine, or methionine residues. It is well known that several amino acids are considered to conservative substitutions of Val. These amino acids include Leu, Ile and Met. Atlas of Protein Sequence and Structure, p. 96, is cited to show that such amino acids are known conservative substitutions of Val (see col. 8). Therefore, in view of the equivalence of Val, Ile, Leu, and Met, the use of Ile, Leu or Met amino acid residues in place of Val in the primary reference would have been obvious to one of ordinary skill in the art at the time the invention was made. One would expect, in the absence of evidence to the contrary, that peptides resulting from substitution of a Val residue in VVRP peptide taught in Kohmura with Ile, Leu, or Met residues will have similar biological activity and thus be also useful in pharmaceutical preparations.

8. Claims 1, 3, 4 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al, supra., and further in view of Bundgaard (Design of Prodrugs, Chapter 1, 1985) and Sumner-Smith (US 5,646,120).

The instant claims, in part defined in claim 1, items (5-7), are drawn to compositions comprising peptide comprising sequence VVRP peptide and having acetyl protective group at N-terminus and/or amido group at C-terminus.

The Kohmura reference is applied as above. It is well known in the peptide art to administer peptide in a form of their prodrugs which have protected N- and/or C- termini because such substitution allows to optimize their solubility and/or stability and make them more suitable for pharmaceutical applications. The most common prodrugs are those requiring a hydrolytic cleavage mediated by enzymatic catalysis. See Bundgaard, p. 1. Sumner-Smith is cited to illustrate use of acetyl group to protect NH_2 terminal group, and amido-group, to protect COOH terminal group in peptides prepared for *in vivo* administration. See col. 2, lines 45-52,col. 6, lines 42-50, 53-62. Therefore, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use peptides described by Kohmura in pharmaceutical compositions in a form of a prodrug analog having protected N- and/or C-termini with a reasonable expectation that such prodrugs will have at least similar effectiveness in inhibition of angiotensin-converting enzyme and regulation of related physiological processes.

9. Claims 1, 3 are rejected under 35 U.S.C. 102(e) as anticipated by Steffens et al. (US Patent 5,681,721).

The instant claims, in part defined in claim 1, item (4), are drawn to compositions comprising protein with molecular weight of between approximately 0.5 and 100 kD, said protein comprising oligopeptide VVRP.

Proteins comprising sequence VVRP are well described in the prior art: Search in Registry file of STN Database produced 396 hits. Steffens et al reference is used as a representative.

Steffens

Steffens teaches bifunctional urokinase variants having improved fibrinolytic characteristics and thrombolytic pharmaceutical compositions comprising thereof. See claims 1, 18. In particular, the reference teaches protein

1 SKTCYEGNGH FYRGKASTDT MGRPCLPWNS ATVLQQTYHA HRSDALQLGL
51 GKHNYCRNPD NRRRPWCYVQ VGLKPLVQEC MVHDCADGKK PSSPPEELKF
101 QCGQKTLRPR FKIIGGEFTT IENQPWFAAI YRRHRGGSVT YVCGGSLISP
151 CWVISATHCF IDYPKKEDYI VYLGRSRLNS NTQGEMKFEV ENLILHKDYS
201 ADTLAHHNDI ALLKIRSKEG RCAQPSRTIQ TICLPSMYND PQFGTSCEIT
251 GFGKENSTDY LYPEQLKMTV VKLISHRECQ QPHYYGSEVT TKMLCAADPQ
301 WKTDSCQGDS GGPLVCSLQG RMTLTGIVSW GRGCALKDKP GVYTRVSHFL
351 PWIRSHTKEE NGLALSPVVV VVRPLGGGGN GDFEEIPEEY LQ

having VVRP moiety at positions 371-374 (underlined). See col. 11, compound M28.
The pharmaceutical composition of Steffens anticipates the instantly claimed composition comprising peptides comprising VVRP sequence as claimed.

10. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Steffens et al., supra., and further in view of Atlas of Protein Sequence and Structure (Vol. 5, 1972).

The instant claims, in part defined in claim 1, items (2), (4), are drawn to compositions comprising protein with molecular weight of between approximately 0.5 and 100 kD, said protein comprising oligopeptide VVRP wherein one of Val residues is replaced by leucine or isoleucine, or methionine residues. It is well known that several amino acids are considered to conservative substitutions of Val. These amino acids include Leu, Ile and Met. Atlas of Protein Sequence and Structure, p. 96, is cited to show that such amino acids are known conservative substitutions of Val (see col. 8). Therefore, in view of the equivalence of Val, Ile, Leu, and Met, the use of Ile, Leu or Met amino acid residues in place of Val in the primary reference would have been obvious to one of ordinary skill in the art at the time the invention was made. One would expect, in the absence of evidence to the contrary, that proteins resulting from substitution of a Val residue in VVRP moiety in the protein taught by Steffens with Ile, Leu, or Met residues will have similar biological activity.

11. Claims 1, 6 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al., supra, or Steffens et al., supra.

The instant claims are drawn to concentration range, 0.000001-10%, of compositions defined in claim 1.

The references are applied as above, see preceding paragraphs 6-10.

In regard to particular concentration ranges of the active ingredient in composition, Kohmura teaches that IC_{50} concentration of the referenced peptides is in the range 8-80μM, which corresponds to about 0.0005 - 0.005% (as compared to 0.000001 - 10% claimed range). Steffens et al use

pharmaceutically effective concentrations (claim 18), which are presented in the reference in concentration units different from those instantly claimed. If there are any differences between Applicant's claimed preparations and that of the prior art, the differences would appear to be minor in nature. The instant invention's preparations, which fall within the scope of the prior art compositions, would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made because, in the absence of sufficient factual evidence or unexpected results to the contrary, Applicant's claims are directed to optimization of an "art recognized variable" which is well within the perview of one of ordinary skill in the art.

Conclusion.

12. No claims are allowed

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Cecilia Tsang can be reached on (703) 308-0254. The fax telephone number for this group is (703) 305-3014. Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

May 21, 1999

MICHAEL BORIN, PH.D
PATENT EXAMINER